difference observed is in part the result of the model systems available for investigation in murine and human systems. The in vivo system that uses genetically modified mice is less stressful than the in vitro cell culture conditions used in human studies, which are more stressful and can induce HRI-ATF4 stress response. For example, using the in vitro culture conditions of the murine erythroid progenitors, HRI-ISR is activated even in iron/heme sufficiency,[5] but it remains inactive in the bone marrow of mice under iron/heme sufficiency.[9] Moreover, murine *Hri*$^{-/-}$ erythroid progenitors exhibit significant inhibition of erythroid differentiation in vitro,[5] whereas *Hri*$^{-/-}$ mice displayed very mild erythroid phenotypes under iron sufficiency.[9]

It is important to note that the foremost function of HRI is to inhibit protein synthesis to mitigate proteotoxicity (see figure). It is this inhibitory effect of HRI in protein synthesis that permits the enhanced translation of *Atf4* mRNA. Increased ATF4 expression is necessary to mitigate oxidative stress in both human and mouse cells. Hahn and Lowrey[10] also reported earlier that HRI-eIF2αP enhanced the translation of γ-globin mRNA. Altogether, HRI kinase seems to have pleiotropic roles in erythropoiesis and hemoglobin synthesis.[2]

In the future, it will be important to investigate the role of the HRI-ISR signaling in humans under more physiological conditions, for example, by examining the association of *Hri* or *Atf4* genes with HbF production in patients with β-thalassemia or sickle cell anemia. In summary, the Huang et al discovery of ATF4 as a downstream target of HRI stress signaling in silencing γ-globin gene transcription advances our understanding of fetal globin gene expression and connects translational regulation by HRI with downstream functional impacts on transcriptional regulation by ATF4. Furthermore, this study broadens our capabilities to develop new therapeutics for β-hemoglobinopathies.

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CLINICAL TRIALS AND OBSERVATIONS

Comment on Wei et al, page 2137

The long road: improving outcome in elderly "unfit" AML?

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In this issue of *Blood*, Wei et al[1] report the results of a prospective randomized placebo-controlled trial that presents formal evidence of an overall survival benefit of adding venetoclax to low-dose cytarabine (LDAC) in elderly patients with newly diagnosed acute myeloid leukemia (AML) not considered eligible for intensive cytotoxic treatment.

The treatment of individuals of older age with AML who are considered not eligible for intensive treatment approaches (often referred to as the "unfit" patients with AML) poses one of the greatest challenges in clinical practice. These patients need treatment other than the commonly applied "7+3"-like intensive remission induction chemotherapy and transplantation. The unmet therapeutic need of these "unfit" older patients has become an area of intense clinical research.

About 15 years ago, a comparative trial demonstrated survival superiority of a regimen of subcutaneous LDAC (20 mg twice daily for 10 days at 4- to 6-week intervals) as compared with hydroxyurea and supportive care in patients aged 60 years or older who were deemed unfit for intensive chemotherapy.[2] Since those days, LDAC has become an accepted approach for the "unfit" patient with AML. The popularity of LDAC has remained limited because of the quantitatively marginal benefit in survival that it offers, and the lack of an apparent therapeutic benefit in the cytogenetically poor-risk subset of AML. The multicenter study reported in this issue of *Blood*[1] used LDAC as the reference treatment in a placebo-controlled prospective 1:2 randomized design in newly diagnosed older patients with AML and demonstrates that the addition of venetoclax to LDAC improves outcome (survival). Based on the reported toxicity profiles, the combination appears practically manageable. Notably, despite quite a large difference in complete response (complete remission [CR]/CR with incomplete hematologic recovery [CRi]) rates (48% vs 13%),

the primary end point of overall survival was not met at the preplanned time of the analysis. However, an unplanned post hoc multivariate analysis controlled for the unequal distribution of prognostic factors at baseline between the 2 study groups (adjusted hazard ratio 0.67) and an unplanned analysis after an additional 6 months revealed a statistically significant survival advantage for the venetoclax-LDAC combination. The weak correlation between the relatively wide differences in comparative CR/CRi rates and the much smaller differences in survival values of both treatments might be due to a limited depth of the complete responses following venetoclax-LDAC therapy or the early development of therapeutic resistance. This study establishes the combination of venetoclax-LDAC as a regimen that is better than LDAC. Consistent with this, various other clinical end points like event-free survival, adherence to continuing on therapy, transfusion independence, patient-reported outcomes, and fatigue also indicated an advantage for the venetoclax-LDAC combination.

Despite these favorable observations, the results are still sobering with a rapid drop of the survival curves to values of ~25% or less within 18 months, and event-free survival rates even falling to considerably lower levels (event-free survival plots not presented in the paper). The increase in median survival from 4.9 to 7.2 (preplanned) or 8.4 months (after longer follow-up) is remarkably less than the 10.1-months value previously reported by the investigators for the same venetoclax-LDAC regimen in a single-arm study.[3] This again reminds us of the importance of carefully conducted prospective comparative trials when we wish to critically assess the value of advances in treatment. Although various previously reported studies dealing with the addition of other therapeutic compounds to LDAC had failed to enhance survival,[4,5] glasdegib, a Hedgehog pathway inhibitor, added to the LDAC regimen, did improve survival in a randomized phase 2 study in so-called "unfit" patients with AML and high-risk MDS with median survival values going up from 4.9 months (LDAC) to 8.8 months (LDAC + glasdegib).[6]

What led the investigators to combine LDAC with venetoclax? Although as yet most of the accumulated experience with venetoclax, an orally available inhibitor of the antiapoptotic molecule BCL2, has been obtained in lymphoid malignancies, the interest in the use of venetoclax in AML has recently spiked. Various studies, although still based on limited numbers of patients in single-arm studies with relatively immature follow-up, suggest promising therapeutic activity. Venetoclax single agent in AML produces a modest overall response rate of 19%,[7] emerging data suggest that venetoclax as an adjunct to other compounds may enhance antileukemic activity. For example, combining venetoclax with a hypomethylating agent (azacitidine or decitabine) leads to encouraging complete response rates (CR/CRi rates of 54% and 67%, respectively).[8] Therefore, the results of a prospective randomized trial concerned with the value of the addition of venetoclax to azacitidine in treatment-naive "unfit" patients with AML, which has completed enrollment, are eagerly awaited (#NCT02993523). Whether the latter and various other alternative venetoclax combinations under investigation have the potential of offering a greater benefit than the LDAC-venetoclax combination reported in the study by Wei et al remains to be seen.

How to properly identify the patients unsuitable for intensive treatment? This question obviously has highly significant relevance for clinical practice. Unfortunately, unambiguous criteria for selecting the "unfit" patients with AML are lacking, and the challenge of rightly identifying the "unfit" patients remains the subject of scientific debate. The framework for nonsuitability for intensive treatment in the current study (the eligibility for enrollment in the trial) was based on age ≥75 years or ≥18 to 74 years of age plus at least 1 criterion associated with lack of fitness for intensive induction chemotherapy, including an Eastern Cooperative Oncology Group (ECOG) performance status of 2 to 3, or particular defined comorbid conditions. By these inclusion criteria, a substantial proportion of the study population might have been not only "unfit," but even "frail" (eg, ~10% of patients had ECOG performance score of 3). This not unlikely indicates a considerable additional level of heterogeneity that impacts meaningful outcome assessments, as some patients might have been too frail to benefit from almost any antileukemic treatment that introduces toxicities.

In summary, there is an urgent need for more effective treatment options for the category of patients with AML who cannot be "safely" offered intensive remission induction chemotherapy. Although various novel developmental avenues currently are actively pursued, the study reported by Wei et al represents a valuable although moderate step forward on the way to a better therapeutic future for the "unfit" patient with AML.

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